matter. Thus, claims 1-5, 11, 12, 34-37 will be pending upon entry of this amendment.

Objection Under 35 U.S.C. §132 - New Matter

The Examiner objected to the amendment filed October 18, 1999 under 35 U.S.C. §132 because it allegedly introduces new matter into the disclosure. The Examiner stated that the added material which is not supported by the original disclosure is as follows: the amendment of "a tumor cell" to a "neuronal tumor cell" is new matter as there is no citation of a neuronal tumor cell in the specification or in the claims as originally filed. Moreover, the Examiner stated that applicants have not indicated where the specification supports "a neuronal tumor cell" in applicants' Response (see page 6 of applicants' Response).

In reply, applicants have amended claim 2 which applicants believe obviates this ground of this objection.

Rejection Under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 1-5, 11 and 12 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that claim 1 is vague and indefinite for the following reasons: it is unclear which cell types are suitable for evaluating neurotoxicity; and it is unclear if the cells endogenously express a receptor for advanced glycation end product protein (RAGE) and a mutant presenilin-2. In addition, the

Examiner stated that the phrase "is capable of" renders the claim vague and indefinite as it is unclear if certain cell culture conditions are required such that the mutant presenilin-2 protein actually causes increased basal apoptosis in nerve growth factor-differentiated PC12 cells. The Examiner stated that it is suggested that applicants amend the phrase "wherein the mutant presenilin-2 protein is capable of causing increased basal apoptosis" to "wherein the mutant presenilin-2 protein causes increased basal apoptosis".

The Examiner stated that claim 4 is rendered vague and indefinite by the phrase "a solid support" as there is no definition or examples of solid supports in the specification. Thus, the Examiner stated that it is unclear what is encompassed by "a solid support".

The Examiner stated that claim 11 is rendered vague and indefinite by the phrase "a compound capable of inhibiting neurotoxicity" as it is unclear if certain conditions are required such that the compound actually inhibits neurotoxicity. The Examiner stated that it is suggested that applicants amend the phrase "a compound actually inhibits neurotoxicity" to "a compound which inhibits neurotoxicity".

In reply, applicants have amended claim 1 as requested by the Examiner and maintain that this amendment obviates this ground of rejection as to claim 1. With regard to "solid support," applicants maintain that the plain language of this claim renders the claim language definite. A solid support is known to one of skill in the art as a material to which a compound can be affixed. For example, applicants attach hereto as Exhibits A-C the following

documents which were published prior to the subject application's filing date which indicate that one of ordinary skill in the art would have known what is meant by "solid support."

A. Backes B. J. and Ellman, J. A. (Jun 1997) Solid support linker strategies. Curr Opin Chem Biol 1(1):86-93 **(Exhibit A)**;

B. Roberge, J.Y. et al. (July 1995) A strategy for convergent synthesis of N-linked glycopeptides on a solid support. Science 269(5221):202-4 **(Exhibit B)**; and

C. Wang, G. T. et al. (Aug 1995) Synthetic chemical diversity: solid phas synthesis of libraries of C2 symmetric inhibitors of HIV protease containing diamino diol and diamino alcohol cores. J. Med Chem 38(16):2995-3002 **(Exhibit C)**.

These documents make clear that one of skill in the art would have know the term "solid support" and therefore, this term as used herein is not vague. Examples of such solid supports would have been known to one of ordinary skill in the art. Applicants have amended claim 11 as requested by the Examiner. Applicants maintain that these amendments obviate the rejections set forth by the Examiner and request that the Examiner reconsider and withdraw these grounds of rejection.

Rejection Under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 1-5, 11, and 12 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a method for evaluating the ability of a compound to inhibit neurotoxicity comprising contacting a neuronal cell or a neuronally

differentiated PC12 cell with a compound, and a pharmaceutical composition for use, *in vitro*, comprising a compound identified by the method, does not reasonably provide enablement for a method for evaluating the ability of a compound to inhibit neurotoxicity comprising contacting any non-neuronal cell with a compound, a compound which is peptidomimetic, a compound which is bound to a solid support, or a pharmaceutical composition for use, *in vivo*. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Examiner stated that the specification defines neurotoxicity as encompassing "the negative metabolic, biochemical and physiological effects on a neuronal cell which may result in a debilitation of the neuronal cellular functions, including but not limited to neuronal cell death." In addition, the Examiner stated that the specification states that "Neurotoxicity may include neuronal cytotoxicity or neuronal cell death. (Emphasis added, see page 15, lines 3-13 of the specification). The Examiner stated that while the specification provides a working example of the method utilizing neuronally differentiated PC12 cells, the specification fails to teach how non-neuronal cells such as glial, microglial, astrocyte, endothelial, and mononuclear cells, can be used in a method for evaluating the ability of a compound to inhibit neurotoxicity as disclosed. The Examiner stated that there is no teaching in the specification of any correlation between the effects of a compound to inhibit neurotoxicity in cultured non-neuronal cells and the effects of the compound in cultured neuronal cells. The Examiner stated that in view of applicants' definition of neurotoxicity, and in view of the lack of teaching with regard

to the relevance of treating a non-neuronal cell with a compound and the ability of that compound to inhibit neurotoxicity, one of ordinary skill in the art would not know how to make and use the invention as claimed with a high expectation of success and without undue experimentation. Thus, the Examiner stated that the scope of the claimed invention is not commensurate in scope with the teachings in the specification.

The Examiner stated that with regard to providing a compound which is a peptidomimetic, the specification does not define what would encompass a suitable petidomimetic, nor does the specification identify any particular peptidomimetic or method for selecting a peptidomimetic which is suitable for use in the method for evaluating neurotoxicity. The Examiner stated that absent any guidance in the specification for selecting peptidomimetics, one of ordinary skill the art would not have high expectation of successfully isolating and utilizing a peptidomimetic in the claimed method without undue experimentation.

The Examiner stated that with regard to utilizing a compound bound to a solid support, the specification does not define what is intended by solid support nor does the specification disclose any solid supports which are suitable for use in the claimed method. In addition the Examiner stated that the specification does not teach the structures or classes of compounds which may be bound to solid supports. The Examiner stated that as the specification does not disclose solid supports or compounds which are suitable for attachment to a solid support, one of ordinary skill in the art would not know which supports to use for which compounds, nor would one of ordinary skill in the art know if any and all compounds are actually capable of binding to solid supports. Thus, the Examiner

stated that one of ordinary skill in the art would not have had a high expectation of successfully ascertaining which particularly compound should be bound to a particular solid support without undue experimentation.

The Examiner stated that claims 11 and 12 are directed to a pharmaceutical composition, wherein the composition comprises a compound which inhibits neurotoxicity and a pharmaceutically acceptable carrier. The Examiner stated that as written, the pharmaceutical composition encompasses both in vitro and in vivo applications. Moreover, the Examiner stated that the compound can encompass macromolecules such as nucleic acids.

The Examiner stated that while the specification is enabling for providing a pharmaceutical composition to neuronal cells in vitro to establish whether the compound inhibits neurotoxicity, the specification is nonenabling for administering a pharmaceutical composition which inhibits neurotoxicity in vivo. The Examiner stated that the specification does not provide any correlation with respect to the in vitro and in vivo effectiveness of a compound as the inhibition of neurotoxicity has only been demonstrated in vitro.

The Examiner stated that the specification broadly discloses neuronal disorders which can be treated by a compound identified by the claim-designated *in vitro* diagnostic method. The Examiner stated that the specification only discloses prophetic examples of administering such a composition to treat humans or animals suffering from neurodegenerative conditions which may be associated with Alzheimer's disease, diabetes, senility, renal failure, hyperlipidemic atherosclerosis, neuronal toxicity, Down's syndrome,

dementia associated with head trauma, amyotrophic lateral sclerosis, myasthenia gravis, multiple sclerosis, neuronal degeneration, spongiform encephalopathic diseases, etc. (See page 10, lines 10-34 of the specification). However, the Examiner stated that the specification does not disclose which compound would be suitable for treating a particular disease, whether the same compound would successfully treat all recited diseases, what dosages and routes of administration of the compound would be effective in treating a specific disclosed disease, and how one would ascertain whether the pharmaceutical composition was effective in ameliorating a specific disclosed disease.

The Examiner stated that it should also be noted that the state of the art at the time of filing indicates that treating neurodegenerative diseases is neither routine nor predictable. The Examiner stated that for example, Sabate et al. (Clinical Neuroscience, 3:317-321, 1996) indicate that while neurotrophic factors have been shown to promote the survival of particular neuronal populations, the use of classical pharmacotherapy for neurological diseases is restricted by constraints specific to the nervous system. The Examiner stated that in particular, the blood-brain barrier prevents access to the brain of numerous macromolecules of therapeutic value. The Examiner stated that delivery of such molecules requires intracerebral or intracerebroventricular injection, and infusion using osmotic pumps when long-term treatments are necessary. Therefore, the Examiner stated that the combination of infectious risks and constraints of the delivery technique have precluded the generalized use of drugs (see page 317, right column, last paragraph, bridging page 318). The Examiner stated that with regard to utilizing pharmaceutical compositions comprising nucleic acids, Sabate et al. indicate that

gene therapy should enable neurologists to overcome the problems raised by pharmacotherapy. However, the Examiner stated that Sabate et al. caution that there are several important issues to be resolved if gene therapy for neurological diseases is to become a reality including (1) extent of transgene expression, (2) stability of transgene expression, (3) targeting of the cells, (4) safety of the procedure, and (5) the vector large-scale production capacity (see page 318, left column, under "Recombinant Adenovirus For Gene Therapy"). The Examiner stated that from the teachings of Sabate et al., it is apparent that the art of pharmacotherapy and gene therapy with respect to treating neurodegenerative diseases is neither routine nor predictable.

The Examiner stated that in view of the lack of guidance in the specification as to which compounds should be included in the pharmaceutical compositions to treat specific neurodegenerative diseases, the modes of administration which would be effective in treating such neurodegenerative diseases, the lack of working examples which show the effectiveness of treating such neurodegenerative diseases, and the unpredictability of successfully treating neurodegenerative diseases with pharmacotherapy and gene therapy, one of ordinary skill in the art would not have had a high expectation of successfully providing a pharmaceutically composition, for in vivo use, which is effective in treating the disclosed neurodegenerative disorders without undue experimentation. Thus, the Examiner stated that while the specification is enabling for a pharmaceutical composition which can be used in *in vitro* applications, the specification is not enabling for a pharmaceutical composition which can be used in *in vivo* applications.

Claimed Invention is Fully Enabled

In reply, applicants traverse the rejection and maintain that the claimed invention is fully enabled by the subject specification. The Examiner has raised a number of concerns regarding the enablement of the claimed invention which applicants believe are not sufficiently supported by evidence. Applicants respectfully point out that the Examiner has the burden to explain why she

> ...doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go tho the trouble and expense of supporting his presumptively accurate disclosure.

In re Marzocchi, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). Therefore, the only relevant question is over the objective truth of the evidence relied upon as support for compliance with the enablement requirement. Applying this standard, applicants have addressed the Examiner's concerns insofar as they may be deemed relevant to the amended claims, in the following remarks.

Applicants' claimed invention is directed, *inter alia*, to a method for evaluating the ability of a compound to inhibit neurotoxicity which comprises: (a) contacting a cell which is transfected with DNA encoding (i) a receptor for advanced glycation end product (RAGE) protein and (ii) a mutant presenilin-2 protein with the compound, wherein the mutant presenilin-2 protein causes increased basal apoptosis in nerve growth factor-differentiated PC12 cells; (b) adding a concentration of amyloid-beta peptide to the cell

culture; (c) determining the level of cell death in the cell culture; and (d) comparing the level of cell death determined in step (c) with the amount determined in the absence of the compound so as to evaluate the ability of the compound to inhibit neurotoxicity.

The Examiner acknowledges that the claimed method is enabled for use *in vitro,* but is concerned that the claimed method is not enabled for use *in vivo*. Applicants maintain that one of ordinary skill in the art would be fully enabled by the subject specification to carry out the claimed method *in vivo*. For example, the claimed method as recited in claim 1 calls for a cell transfected with DNA encoding RAGE and mutant PS-2. Applicants emphasize that this cell could be part of an organism and that the claimed method could be carried out *in vivo* by routine methods. For example, one of ordinary skill would be able to make, by routine methods, a transgenic mouse which has been engineered with a DNA construct which encodes RAGE and a mutant PS-2. The mouse could then be administered a test compound so that the compound contacts a cell within the mouse and then the mouse could be administered a concentration of amyloid-beta peptide. This administration could be carried out via perfusion of the brain, cranial injection, etc. (all routine methods). Finally, the mouse could be sacrificed and the cells be surveyed for cell death (by histological staining, by microscopy, etc.) or alternatively, a non-invasive method could be utilized to determine the level of cell death. Clearly, the application of the claimed method to *in vivo* use would be routine to one of ordinary skill in the art.

The Examiner also alleged that the specification "fails to teach how non-neuronal cells, such as glial, microglial, astrocyte,

endothelial and mononuclear cells, can be used in a method for evaluating the ability of a compound to inhibit neurotoxicity as disclosed." In reply, applicants point out that there are many cell types which are located in the neural system of an organism and these cells work together. The Examiner characterizes glial cells, microglial cells, astrocytes, endothelial cells, and mononuclear cells as "non-neuronal" cells and therefore, allegedly irrelevant to "neurotoxicity." Applicants point out that all of the aforementioned cell types are found in neural tissues (brain tissues) of organisms and therefore, are relevant to neurotoxicity. For example, applicants provide examples from the scientific literature prior to the filing date of the subject application, which clearly shows that one of ordinary skill in the art would have known these cells to be important in neuronal functions.

D. Kochi, S. et al. Life Science 2000, 66(23):2255-60 which discloses induction of apoptosis in mouse brain capillary endothelial cells by cyclosporin A and tacrolimus. The data presented by the authors suggest that the induction of apoptosis on the brain capillary endothelial cells may be at least partly involved in neurotoxicity and encephalopathy. **(Exhibit D)**;

E. Hirase, T. et al. J. Cell Sci (Jul 1997) 110(Pt 4):1603-13. This document discloses a transmembrane protein, occludin, which is a possible determinant of tight junction permeability in endothelial cells. Applicants point out that the authors characterize endothelial cells as a part of neuronal tissue (see abstract) **(Exhibit E)**.

The Examiner took the position that the method claimed is not

enabled for any non-neuronal cell. The Examiner alleged that the specification does not provide any correlation between the effects of a compound to inhibit neurotoxicity in cultured non-neuronal cells and the effects of the compound in cultured neuronal cells. The claimed method is enabled for either neuronal cells or non-neuronal cells. Since, as addressed *supra*, the other cells listed in the specification are involved with neuronal function and make up integral parts of the brain, the claimed method which utilizes a non-neuronal cell (albeit a related and relevant cell to neuronal function) will produce a result which is relevant to inhibiting neurotoxicity. The definition of "neurotoxicity" which is recited in the specification includes "debilitation of neuronal cellular functions" and "negative metabolic, biochemical and physiological effects on a neuronal cell...." Therefore, debilitation of the functioning of any of the cell types listed in the specification would result in neurotoxicity. Therefore, the claimed method which utilizes non-neuronal cells is fully enabled and the method would provide a relevant result.

The Examiner is also concerned that peptidomimetic is not defined a suitable peptidomimetic. Applicants emphasize that peptidomimetics would have been fully known to one of ordinary skill in the art at the time of filing of the subject application. The making of peptidomimetics is discussed at length in U.S. Patent No. 5,612,895, issued March 18, 1997, entitled "Method of rational drug design based on ab initio computer simulation of conformational features of peptides." A peptidomimetic is a peptide which has been modified in order to prevent degradation, increase half-life, decrease toxicity and increase bioavailability. The naturally occurring amino acid residues are replaced with synthetic or non-naturally occurring groups which prevent the

degradation of the molecules. A peptidomimetic is one possible type of compound which could be evaluated as inhibiting neurotoxicity by the claimed method. There are many possible "suitable" peptidomimetics which would be encompassed by the claimed invention. Applicants maintain that the Examiner has not provided any evidence that applicants' specification is not enabled for peptidomimetics and in view of the above discussion maintains that the specification is fully enabling.

With regard to the Examiner's concern regarding "solid support," applicants maintain that the plain language of the claim and the specification is sufficient to enable the claimed invention. A solid support would have been known to one of ordinary skill in the art at the time. There are many types of materials to which a compound could be affixed. Applicants emphasize that a particular solid support, would be known by one of ordinary skill to be suitable for a particular type of compound. For example, certain compounds are know to bond well to silica type materials, other compounds are know to bind well to plastics, still other materials are known to bind well to metals. Applicants point out that there is no evidence provided by the Examiner to support her position. Clearly, the specification is enabling for the words "solid support." Applicants also refer the Examiner to the discussion of "solid support" under the section hereinabove regarding rejection under 35 U.S.C. §112, second paragraph.

Next, the Examiner alleges that the specification is non-enabling for administration of a pharmaceutical composition which inhibits neurotoxicity *in vivo*. Applicants emphasize that the Examiner has again, provided no support for this position. In fact, the administration of compounds which would inhibit neurotoxicity would

have been well known to one of ordinary skill in the art. For example, applicants refer the Examiner to the reference attached hereto as **Exhibit D** wherein cyclosporin A, which is shown to inhibit neurotoxicity, is administered to a subject. In addition, it would have been routine for one of ordinary skill in the art to take a compound which is identified as an inhibitor of neurotoxicity *in vitro* or *in vivo*, to obtain a pharmaceutical composition as claimed in claim 11. Specifically, it is routine optimization known to one of ordinary skill in the art to formulate a compound into an acceptable pharmaceutical composition. Dosages, routes of administration and which particular compounds would be useful for which particular disease would all be steps in routine optimization that any would be known to one of ordinary skill in the art. For example, applicants submit herewith as **Exhibit F**, the table of contents from "Biological Approaches to the Controlled Delivery of Drugs" (1987) Annals of the New York Academy of Sciences.

In addition, applicants point out that courts have recognized that determining an effective dosage for a pharmaceutical agent against a particular disease indication is well within the ordinary skill of the art. See *Carter-Wallace, Inc. v Davis-Edwards Pharmacal Corp.*, 341 F. Supp. 1303, 173 USPQ 65 (E.D.N.Y. 1972), aff'd, 176 USPQ2d, 176 USPQ 452 (2nd Cir 1972) cert. denied, 412 U.S. 929 (1973). Obtaining FDA approval for a particular novel pharmaceutical composition is not a short process, however, it is a process which is routine and known to one of ordinary skill. Applicants point out that the FDA approval process is not the standard for patentability.

The Examiner refers to Sabate et al. and alleges that treating

neurodegenerative diseases is neither routine or predictable. Applicants point out that there are no claims pending to "treatment of neurodegenerative diseases," however, applicants maintain that the pharmaceutical composition recited in claim 11 is fully enabled by the subject specification. The Examiner states that the blood-brain barrier (BBB) "prevents access to the brain of numerous macromolecules of therapeutic value." However, applicants maintain that the BBB is merely one challenge in optimizing administration of an inhibitor of neurotoxicity. For example, intracranial implants or injections are possible modes of administration which could be successful.

Finally, the Examiner is concerned that there is an alleged "lack of guidance in the specification as to which compounds should be included in the pharmaceutical composition...." Applicants point out that the method recited in claim 1 is directed to evaluating whether a compound is an inhibitor of neurotoxicity. Therefore, the claimed method itself will produce a result which allows one to determine which compounds would be included in a pharmaceutical composition. The specification is fully enabling for the practice of the claimed invention.

In summary, based on the discussion above and attached Exhibits, applicants urge that the degree of experimentation needed to practice the claimed invention is well within the amount of experimentation that is willingly and routinely undertaken by those of ordinary skill in the relevant arts. Such experimentation, which is guided by applicants' disclosure viewed in light of earlier studies, is very clearly not undue. In re Wands, 8 USPQ 2d 1400, 1406-1407 (Fed. Cir. 1988).

It is well settled law that enablement is not precluded by the necessity for some experimentation. In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The key word in this regard is "undue" not "experimentation." Id., citing in re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). Thus

> [t]he determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the claimed invention and the state of the art. [citations omitted] The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Wands at 1404, citing in re Jackson, 217 U.S.P.Q. 804, 807 (B.P.A.I. 1982).

Applicants' specification in combination with what was known to one of skill in the art as of the effective filing date (i.e., December 23, 1997) would have enabled the skilled person to carry out the presently claimed invention without undue experimentation. The rejection should therefore be reconsidered and withdrawn.

Rejection Under 35 U.S.C. §102(b) - Wolozin et al. in light of Brett et al.

The Examiner rejected claims 1-3, 5, 11 and 12 under 35 U.S.C. §102(b) as being anticipated by Wolozin et al. (Science, 274: 1710-1713, December 6, 1996, newly applied) in light of Brett et al. (Amer. J. Pathol., 143: 1699-1712, 1993, newly applied).

The Examiner stated that Wolozin et al. disclose that transfecting neuronally differentiated PC12 cells with a mutant presenilin-2 protein causes increased basal apoptosis in nerve growth factor-differentiated PC12 cells (see, e.g., page 1711, middle column, and Figure 1). In addition, the Examiner stated that Wolozin et al. disclose a method comprising a) culturing the neuronally differentiated PC12 cells in the presence or absence of a compound, i.e., pertussis toxin or amyliod-beta (1-42), b) determining the level of apoptosis in the control and treated cells, and c) comparing the extent of apoptotic activity in the cells cultured in the absence of the compound to evaluate the effect of the compound on apoptotic activity (see, e.g., page 1711, middle and right columns, page 1712, left column, Figure 3, and Figure 4E). The Examiner stated that the amyloid-beta(1-42) compound is added to the cells at a concentration of 10 M and was generated from a 1 mM A (1-42) stock solution (see, e.g., page 1713, Note #21). Thus, the Examiner stated that Wolozin et al. disclose the claimed method and pharmaceutical carrier. The Examiner stated that it is noted that PC12 cells inherently express a receptor for advanced glycation end product protein (see Brett et al., page 1760, left column).

Thus, the Examiner stated that the method and pharmaceutical composition disclosed by Wolozin et al. anticipates the claimed invention.

In reply, applicants traverse the rejection and maintain that Wolozin et al. in view of Brett et al. do not anticipate the claimed invention.

The claimed invention is directed to, *inter alia*, a method for

evaluating the ability of a compound to inhibit neurotoxicity which comprises: (a) contacting a cell which is transfected with DNA encoding (i) a receptor for advanced glycation end product (RAGE) protein and (ii) a mutant presenilin-2 protein with the compound, wherein the mutant presenilin-2 protein causes increased basal apoptosis in nerve growth factor-differentiated PC12 cells; (b) adding a concentration of amyloid-beta peptide to the cell culture; (c) determining the level of cell death in the cell culture; and (d) comparing the level of cell death determined in step (c) with the amount determined in the absence of the compound so as to evaluate the ability of the compound to inhibit neurotoxicity.

Wolozin et al. do not anticipate the claimed invention for several reasons. First, Wolozin et al. do not disclose a cell which is transfected with DNA which encodes RAGE and mutant PS2 as presently claimed. Brett et al. discloses that PC12 cells which are obtained from a Dr. L. Greene (see page 1702, column 2, 1st paragraph of Brett et al.) and which were derived from a transplantable adrenal medullary pheochromocytoma express RAGE specifically after being subjected to NGF in culture at a concentration of 10 nM for 48 hours. Wolozin et al., on the other hand, do not specify the origin of the PC12 cells utilized therein. Wolozin et al. recites that the PC12 cells are maintained in medium containing NGF at 100 ng/ml for 24 hours. These conditions are different than the conditions recited in Brett et al. The Wolozin et al. reference does not indicate whether the PC12 cells used therein express RAGE at all. Nevertheless, the claimed invention now makes clear that the cells utilized in the method are transfected with DNA which encodes RAGE and mutant PS2. Wolozin et al. do not disclose any cell which is transfected with DNA which encodes RAGE and mutant

PS2. Indeed, the cells disclosed in Wolozin et al. are not transfected with DNA encoding RAGE. Therefore, Wolozin et al. do not anticipate the claimed invention.

Furthermore, Wolozin et al. do not disclose a method comprising the steps as presently claimed. There is no disclosure in Wolozin et al. of contacting a cell (as recited in claim 1) with a test compound, followed by addition of amyloid-beta peptide to the cell culture as claimed (see steps (b) and (c) of claim 1). The Examiner points to a portion of Wolozin et al. in which pertussis toxin or an amyloid-beta peptide is added to PC12 cells in culture and then apoptosis is observed. In neither case are all of the steps of the claimed method disclosed. Although the Examiner analogizes the addition of pertussis toxin to the addition of a compound as claimed, there is no step in which Wolozin et al. add a concentration of amyloid-beta peptide to that cell culture. Similarly, although Wolozin et al. discloses addition of an amyloid-beta peptide to cells transfected with PS2, there is no disclosure of the step of contacting those cells with a compound to be tested. In any event, the cells used in this experiment are not transfected with DNA encoding RAGE as presently claimed. Therefore, Wolozin et al. do not anticipate the claimed invention.

Finally, the claimed method is a screening method for evaluating the ability of a compound to inhibit neurotoxicity. Wolozin et al. do not disclose such a method. Wolozin et al. do not disclose any evaluation of any compounds as to their ability or inability to inhibit neurotoxicity.

For these reasons, applicants request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §102(b) - Bartus et al.

The Examiner stated that claims 11 and 12 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Bartus et al. (U.S. Patent No. 5,444,042, 1995) for the reasons of record set forth in the Office Action of 4/13/99 (Paper No. 7), and the reasons below.

The Examiner stated that the claims are directed to a pharmaceutical composition comprising a compound capable of inhibiting neurotoxicity, claimed in a product-by-process format.

The Examiner stated that Bartus et al. disclose that calpain activation is an event central to many cases of brain atrophy and degeneration and that inhibition of calpain alone is sufficient to inhibit or prevent cell deterioration and loss (see column 6, lines 16-23). The Examiner stated that Bartus et al. teach compounds which inhibit neurotoxicity, i.e., calpain inhibitors. The Examiner stated that the calpain inhibitors effectively block cell death in an *in vitro* model for neuropathology (see column 73, lines 5-24). The Examiner stated that the compounds can be formulated as pharmaceutical compositions comprising the compound of interest in a pharmaceutically acceptable formulation containing a carrier material (see column 4, lines 48-54 and column 66, lines 36-40). Thus, the Examiner stated that the pharmaceutical composition disclosed by Bartus et al. anticipates the claimed invention.

In reply, applicants traverse the rejection. Bartus et al. do not anticipate the claimed invention as recited in claim 11 as follows: a pharmaceutical composition which comprises a compound which inhibits neurotoxicity identified by the method of claim 1, and a pharmaceutically acceptable carrier.

The pharmaceutical composition disclosed by Bartus et al. was not identified by the method recited in claim 1 as is required by claim 11. Bartus et al. do not disclose inhibitors of calpain activation which are identified by the method recited in claim 1. Bartus et al. do not disclose a method for evaluating the ability of a compound to inhibit neurotoxicity which comprises: (a) contacting a cell which is transfected with DNA encoding (i) a receptor for advanced glycation end product (RAGE) protein and (ii) a mutant presenilin-2 protein with the compound, wherein the mutant presenilin-2 protein causes increased basal apoptosis in nerve growth factor-differentiated PC12 cells; (b) adding a concentration of amyloid-beta peptide to the cell culture; (c) determining the level of cell death in the cell culture; and (d) comparing the level of cell death determined in step (c) with the amount determined in the absence of the compound so as to evaluate the ability of the compound to inhibit neurotoxicity as presently claimed.

The Examiner pointed out that Bartus et al. "teach a method of evaluating the ability of a compound to inhibit neurotoxicity comprising treating N18-RE-105 cells with calpain inhibitors and measuring the extent of cell death." (See April 13, 1999 Office Action.) Bartus et al. do not anticipate the claimed invention for several reasons. First, the calpain inhibitors are not identified by the method recited in present claim 1. N18-RE-105 cells are not transfected with DNA encoding RAGE and mutant PS2 as recited in claim 1. In addition, there is no disclosure in Bartus et al. of the step of adding a concentration of amyloid-beta peptide to the cell culture prior to making a determination of the level of cell death in the culture (see step (c), claim 1).

For the foregoing reasons, applicants maintain that Bartus et al. do not anticipate the claimed invention. Applicants request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §103(a)

The Examiner stated that claims 1, 3, 11, and 12 are rejected under 35 U.S.C. §103(a) as being unpatentable over Wolozin et al. (Science, 274:1710-1712, 1996, newly applied).

The Examiner stated that the claimed invention is drawn to a method of evaluating the ability of a compound to inhibit neurotoxicity and pharmaceutical compositions comprising compounds identified by the method.

The Examiner stated that Wolozin et al. disclose a method of evaluating the ability of a compound to inhibit neurotoxicity utilizing neuronally differentiated PC12 cells which intrinsically express a receptor for advanced glycation end protein as disclosed by Brett et al., and as discussed in the 35 U.S.C. 102(b) rejection above.

The Examiner stated that Wolozin et al. do not disclose adding a nucleic acid compound to neuronally differentiated PC12 cells expressing a mutant presenilin-2 protein, or all of the claim-designated pharmaceutical carriers.

However, the Examiner stated that Wolozin, et al. disclose adding PS-2 or ALG-3 antisense nucleic acids to neuronally differentiated PC12 cells which do not express a mutant presenilin-2 protein. The Examiner stated that addition of the antisense nucleic acid results

in a decrease in apoptotic activity in the PC12 cells (see, e.g., pge 1720, middle and right columns, and Figure 1). The Examiner stated that inasmuch as Wolozin et al. disclose that PC12 cells that express a mutant presenilin-2 protein having a high apoptotic activity, it would have been obvious to add PS-2 or ALG-3 antisense nucleic acids to neuronally differentiated PC12 cells expressing mutant presenilin-2 to determine if the antisense nucleic acids are effective in decreasing the observed apoptotic activity in PC12 cells expressing mutant presenilin-2 protein.

The Examiner stated that with regard to pharmaceutical compositions comprising a compound and a pharmaceutically acceptable carrier, although Wolozin et al. do not disclose that the nucleic acid compounds, pertussis toxin compound or amyloid-beta peptide (1-42) compound is admixed with all of the claim-designated pharmaceutical carriers, it is well established in the art of cell culture to admix compounds with solutions containing water, buffers, salts, or other suitable carriers prior to adding the compound of interest to the culture. The Examiner stated that one of ordinary skill in the art would have been motivated to admix the compound of interest with a suitable carrier to the cell culture and to avoid a localized high concentration of solid compound which may be detrimental to the cells.

The Examiner stated that it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made to modify the method of Wolozin, et al. by substituting the peptide compounds added to the mutant presenilin-2 expressing PC12 cells with nucleic acid compounds such as antisense PS-2 or ALG-3 to determine the ability of these compounsd to inhibit neurotoxicity. The Examiner stated that as Wolozin, et al. was

successful in evaluating the effect of these compounds on mutant presenilin-2 expressing PC12 cells without undue experimentation. Moreover, the Examiner stated that adding the nucleic acids, or other compounds such as pertussis toxin or amyloid-beta peptide (1-42) to cell cultures as a pharmaceutical composition would have been obvious and well within the purview of one of ordinary skill in the art of cell culture for the reasons set forth above.

In reply, applicants traverse the rejection. Wolozin et al. in combination with Brett et al. do not make obvious the claimed invention.

Applicants' invention is directed to a method for evaluating the ability of a compound to inhibit neurotoxicity which comprises: (a) contacting a cell which is transfected with DNA encoding (i) a receptor for advanced glycation end product (RAGE) protein and (ii) a mutant presenilin-2 protein with the compound, wherein the mutant presenilin-2 protein causes increased basal apoptosis in nerve growth factor-differentiated PC12 cells; (b) adding a concentration of amyloid-beta peptide to the cell culture; (c) determining the level of cell death in the cell culture; and (d) comparing the level of cell death determined in step (c) with the amount determined in the absence of the compound so as to evaluate the ability of the compound to inhibit neurotoxicity.

First, the Examiner states that the PC12 cells disclosed by Wolozin et al. "intrinsically express a receptor for advanced glycation endproduct protein...." However, applicants refer the Examiner to remarks regarding the rejection under 35 U.S.C. §102(b) (Wolozin et al. in view of Brett et al.) herein above. Specifically, there is no evidence in Wolozin et al. which indicates that the PC12 cells

used therein express RAGE. More importantly, there is no disclosure in Wolozin et al. (even in view of Brett et al.) of cells which are transfected with DNA encoding RAGE and mutant PS-2 as recited in step (a) of claim 1. There is no hint or suggestion in Wolozin et al. that PS-2 is involved in any way with RAGE receptor proteins. Therefore, there is no suggestion to one of ordinary skill to carry out step (a) of the claimed invention.

Second, the Examiner states that "it would have been obvious to add PS-2 or ALG-3 antisense nucleic acids to neuronally differentiated PC12 cells expressing mutant presenilin-2 to determine if the antisense nucleic acids are effective in decreasing the observed apoptotic activity in PC12 cells expressing mutant presenilin-2 protein." Applicants emphasize that the addition of such antisense molecules as disclosed in Wolozin et al. does not render obvious the now claimed invention. The Examiner is correlating the antisense molecules with the compound recited in claim 1. However, the actual step (a) recited in claim 1 is not made obvious by the disclosure of Wolozin et al. Specifically, "neuronally differentiated PC12 cells expressing mutant presenilin-2" do not make obvious the cells recited in step (a) of claim 1 which are transfected with DNA encoding RAGE and mutant PS-2. There is no recognition in Wolozin et al. of the existence of or significance of an interaction between RAGE and PS-2.

In addition, applicants' invention is not made obvious by Wolozin et al. because there is no teaching or suggestion of all of the steps of claim 1. In particular, there is no teaching of the cells recited in step (a) and there is no teaching or suggestion of adding a concentration of an amyloid-beta peptide to the cell culture as recited in new step (b). It is applicants' invention

which has shown that presenilin-2 couples with the signal transduction system of the RAGE receptor and this is not suggested at all or made obvious by Wolozin et al. in view of Brett et al.

Finally, applicants maintain that there is no motivation to combine the Wolozin et al. disclosure with Brett et al. The only common thread between the two references is the use of PC12 cells as a model system and these cells are in use in many different types of studies and would not direct one of ordinary skill to read Brett et al. after reading Wolozin et al. Brett et al. (published in 1993) discloses a survey of the distribution of a "newly characterized receptor for advanced glycation end products in tissues" (RAGE). There is no mention or suggestion of the PS-2 gene or protein in Brett et al. Moreover, Wolozin et al. do not disclose that RAGE is expressed on the PC12 cells used therein and the conditions under which the PC12 cells are grown in Wolozin et al. are not the conditions specified by Brett et al. for expression of the RAGE receptor. It appears that the Examiner has applied hindsight in combining the Wolozin et al. reference with Brett et al., because without knowing applicants' invention *a priori*, one of ordinary skill would have no motivation to combine Wolozin et al. with Brett et al.

The Examiner has not given a reason why one of ordinary skill in the art would have been motivated to combine these references. Applicants request the Examiner to consider a recent Federal Circuit decision, In re Rouffet, 47 USPQ2d 1453 (Fed. Cir. 1998) which states:

> To prevent the use of hindsight, this court requires the examiner to show a motivation to combine the references that create the

> obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select elements from the cited prior art for combination in the manner claimed.

Applicants submit that the Examiner is using impermissible hindsight in combining the cited references. The Federal Circuit has stated that

> rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability.

Sensonics, Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570, 38 USPQ2d 1551, 1554 (Fed. Cir. 1996). In addition, the Federal Circuit has held that it will infer the use of hindsight in the selection of references that comprise the case of obviousness without an explanation of the specific understanding or principle within the knowledge of one of ordinary skill in the art that would motivate one with no knowledge of the claimed invention to make the combination. See *In re Gorman*, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). Finally, the Federal Circuit stated that if such "a rote invocation [of high level of skill in the art] could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technical advance." See *In re Rouffet*, 47 USPQ2d 1453, 1458 (Fed.

Cir. 1998).

In view of these remarks, applicants maintain that Wolozin et al. (in combination with Brett et al.) do not render obvious the claimed invention. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

No fee other than the $435.00 three-month extension of time fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Jane M Love

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Jane M Love 6/30/00

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